IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Constance A. Bell et al.	Art Unit	: 1637
Serial No.	: 10/068,238	Examiner	: Teresa E. Strzelecka
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Title	: DETECTION OF BACILLUS ANTHRACIS		

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BRIEF ON APPEAL

(1) Real Parties in Interest

The real parties in interest are Mayo Foundation for Medical Education and Research and Roche Molecular Systems, Inc.

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(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 57, 66, 67, 70, 79, 80, 83, 92, 93, and 96 are pending, and stand finally rejected in the Final Office Action mailed January 24, 2008. Claims 1-56, 58-65, 68, 69, 71-78, 81, 82, 84-91, 94, and 95 were previously cancelled without prejudice. Applicants hereby appeal the final rejection of claims 57, 66, 67, 70, 79, 80, 83, 92, 93, and 96.

(4) Status of Amendments

All amendments have been entered.

(5) Summary of Claimed Subject Matter

In general, claims 57, 66, 67, 70, 79, 80, 83, 92, and 93 are directed toward articles of manufacture that comprise two specific primers and two specific probes. Claim 96 is directed toward articles of manufacture that comprise six specific primers and six specific probes.

Claims 57, 66, and 67 are directed toward articles of manufacture that comprise a pair of *capB* primers, a pair of *capB* probes, and a donor fluorescent moiety and a corresponding acceptor fluorescent moiety. See, for example, page 12, lines 5-11, and page 16, line 25 to page 17, line 15. The pair of *capB* primers includes a first *capB* primer consisting of the sequence 5'- CCC AAT TCG AGT AAA CAT A-3' (SEQ ID NO:1) and a second *capB* primer consisting of the sequence 5'- ACT GCC ATA CAT TCA CAA -3' (SEQ ID NO:2), and the pair of *capB* probes includes a first *capB* probe consisting of the sequence 5'- CGA TTA AGC GCC GTA AAG AAG GTC CTA ATA TC -3' (SEQ ID NO:3) and a second *capB* probe consisting of the sequence 5'- GTG AGC AAC GCA GGG TAG TTA AAG AGG CTG -3' (SEQ ID NO:4). See Applicants' specification at, for example, page 12, line 12 to page 13, line 6. The particular primer or probe sequences recited in claims 57, 66, and 67 also can be found, for example, in Table 1 at page 28.

Claims 70, 79, and 80 are directed toward articles of manufacture that comprise a pair of *pagA* primers, a pair of *pagA* probes, and a donor fluorescent moiety and a corresponding acceptor fluorescent moiety. See, for example, page 12, lines 5-11, and page 16, line 25 to page 17, line 15. The pair of *pagA* primers includes a first *pagA* primer consisting of the sequence 5'- TAC AGG ACG GAT TGA TAA G-3' (SEQ ID NO:5) and a second *pagA* primer consisting of the sequence 5'- TTT CAG CCC AAG TTC TTT -3' (SEQ ID NO:6), and the pair of *pagA* probes includes a first *pagA* probe consisting of the sequence 5'- AGT ACA TGG AAA TGC AGA AGT G -3' (SEQ ID NO:7) and a second *pagA* probe consisting of the sequence 5'- ATG CGT CGT TCT TTG ATA TTG GT -3' (SEQ ID NO:8). See Applicants' specification at, for example, page 12, line 12 to page 13, line 6. The particular primer or probe sequences recited in claims 70, 79, and 80 also can be found, for example, in Table 1 at page 28.

Claims 83, 92, and 93 are directed toward articles of manufacture that comprise a pair of *lef* primers, a pair of *lef* probes, and a donor fluorescent moiety and a corresponding acceptor

fluorescent moiety. See, for example, page 12, lines 5-11, and page 16, line 25 to page 17, line 15. The pair of *lef* primers includes a first *lef* primer consisting of the sequence 5'-TTT TAC CGA TAT TAC TCT CC-3' (SEQ ID NO:9) and a second *lef* primer consisting of the sequence 5'- AAC CTA AAG GCT TCT GC -3' (SEQ ID NO:10), and the pair of *lef* probes includes a first *lef* probe consisting of the sequence 5'- ATT AAG GAA TGA TAG TGA GGG T -3' (SEQ ID NO:11) and a second *lef* probe consisting of the sequence 5'- TAT ACA CGA ATT TGG ACA TGC T -3' (SEQ ID NO:12). See, for example, Applicants' specification at page 12, line 12 to page 13, line 6. The particular primer or probe sequences recited in claims 83, 92, and 93 can be found, for example, in Table 1 at page 28.

Claim 96 is directed toward an article of manufacture that comprises a pair of *capB* primers, a pair of *capB* probes, a pair of *pagA* primers, a pair of *pagA* probes, a pair of *lef* primers, and a pair of *lef* probes. The pair of *capB* primers includes a first *capB* primer consisting of the sequence 5'-CCC AAT TCG AGT AAA CAT A-3' (SEQ ID NO:1) and a second *capB* primer consisting of the sequence 5'-ACT GCC ATA CAT TCA CAA-3' (SEQ ID NO:2), and the pair of *capB* probes includes a first *capB* probe consisting of the sequence 5'-CGA TTA AGC GCC GTA AAG AAG GTC CTA ATA TC-3' (SEQ ID NO:3) and a second *capB* probe consisting of the sequence 5'-GTG AGC AAC GCA GGG TAG TTA AAG AGG CTG-3' (SEQ ID NO:4). The pair of *pagA* primers includes a first *pagA* primer consisting of the sequence 5'-TAC AGG ACG GAT TGA TAA G-3' (SEQ ID NO:5) and a second *pagA* primer consisting of the sequence 5'-TTT CAG CCC AAG TTC TTT-3' (SEQ ID NO:6), and the pair of *pagA* probes includes a first *pagA* probe consisting of the sequence 5'-AGT ACA TGG AAA TGC AGA AGT G- 3' (SEQ ID NO:7) and a second *pagA* probe consisting of the sequence 5'-ATG CGT CGT TCT TTG ATA TTG GT- 3' (SEQ ID NO:8). The pair of *lef* primers includes a first *lef* primer consisting of the sequence 5'-TTT TAC CGA TAT TAC TCT CC-3' (SEQ ID NO:9) and a second *lef* primer consisting of the sequence 5'-AAC CTA AAG GCT TCT GC-3' (SEQ ID NO:10), and the pair of *lef* probes includes a first *lef* probe consisting of the sequence 5'-ATT AAG GAA TGA TAG TGA GGG T- 3' (SEQ ID NO:11) and a second *lef* probe consisting of the sequence 5'-TAT ACA CGA ATT TGG ACA TGC T- 3' (SEQ ID NO:12). See, page 12, line 5 to page 13, line 6, and Table 1 at page 28.

(6) Grounds of Rejection to be Reviewed on Appeal

(A) Claims 57, 66, and 67 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over the Ramisse et al. reference[1], the Makino et al. reference,[2] and the Buck et al. reference,[3] and further in view of the Wittwer et al. reference[4] and the Qi et al. reference.[5] The Examiner asserted that while the Ramisse et al. reference teaches primers for detection of the *capB* gene but does not specifically teach the claimed oligonucleotides having SEQ ID NOs:1-4, the Makino et al. reference discloses a *capB* sequence containing regions that are complementary to the claimed SEQ ID NOs:1-4. The Examiner alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to use the method of Ramisse et al. with "functionally equivalent primers" based on the sequence of Makino et al., since Ramisse et al. expressly teach primer selection for *B. anthracis* detection using commercially available software and the *B. anthracis* published sequences and since Makino et al. provide such published sequences for the software program to analyze. Page 4 of the Office Action mailed January 24, 2008. In addition, the Examiner alleged that a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties (page 5 of the January 24, 2008 Office Action), and that the Buck et al. reference provides direct evidence that all primers, and in particular, all primers selected according to the ordinary criteria, however different, would be expected to function (page 5 of the January 24, 2008 Office Action).

The Examiner further cited *In re Deuel*[6] to support the obviousness rejection. In *In re Deuel*, the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. The Examiner noted that, with regard to structural or functional homologs, the Court stated the following:

> Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often

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[1] Ramisse et al. (1996) *FEMS Microbiology Letters* 145:9-16 (Exhibit A)
[2] Makino et al. (1989) *J. Bacteriol.* 171:722-30 (Exhibit B)
[3] Buck et al. (1999) *Biotechniques* 27:528-36 (Exhibit C)
[4] Wittwer et al. (1997) *Biotechniques* 22:130-138 (Exhibit D)
[5] Qi et al. (2001) *Appl. Env. Microbiol.* 67:3720-3727 (Exhibit E)
[6] *In re Deuel*, 51 F.3d 1552, 34 USPQ 2d 1210 (Fed. Cir. 1995)

have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.

The Examiner then asserted that the claimed primers "simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of *B. anthracis*," and alleged that the recited primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations. Page 5 of the January 24, 2008 Office Action.

With further regard to claims 57 and 66, the Examiner asserted that the Wittwer et al. reference teaches dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor, and that the Qi et al. reference teaches real-time PCR detection of *B. anthracis* using two primers and two probes with sequences complementary to the *rpoB* gene, where one probe is labeled with a fluorescent donor and the other with the fluorescent acceptor. The Examiner alleged that given the teachings of the cited references, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to fluorescently label *B. anthracis* detection probes with donor and acceptor moieties. Page 6 of January 24, 2008 Office Action.

(B) Claims 70, 79 and 80 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Ramisse et al. reference (*supra*), the Price et al. reference,[7] and the Buck et al. reference (*supra*), and further in view of the Wittwer et al. reference (*supra*) and the Qi et al. reference (*supra*). The Examiner asserted that the Ramisse et al. reference teaches primers for detection of *pagA* gene, but does not specifically teach oligonucleotides with SEQ ID NOS:5-8. The Examiner further asserted, however, that the Price et al. reference discloses a *pagA* sequence containing regions that are complementary to SEQ ID NOS:5-8. Further, the Examiner stated that the Price et al. reference teaches primers for amplification of *pagA* gene that were designed from published *pagA* sequence.

The Examiner essentially reiterated the allegations set forth above with respect to claims 57, 66, and 67, alleging that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the method of Ramisse et al. with the use of "functionally equivalent primers" selected from the sequence of Price et al. In addition, the Examiner again alleged that the Buck

[7] Price et al. (1999) *J. Bacteriol.* 181:2358-2362 (Exhibit F)

et al. reference expressly provides evidence of the equivalence of primers, and referred to *In re Deuel* (*supra*) to support the assertion that the claimed primers "simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of *B. anthracis*." Sentence bridging pages 8 and 9 of the January 24, 2008 Office Action. With respect to claims 70 and 79, the Examiner repeated the above rejection related to the Wittwer et al. and Qi et al. references, and again asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to fluorescently label *B. anthracis* detection probes with donor and acceptor moieties.

(C) Claims 83, 92 and 93 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Ramisse et al. reference (*supra*), the Bragg et al. reference,[8] and the Buck et al. reference (*supra*), and further in view of the Wittwer et al. reference (*supra*) and the Qi et al. reference (*supra*). The Examiner alleged that the Ramisse et al. reference teaches primers for detection of *lef* gene, and that while the Ramisse et al. reference does not specifically teach oligonucleotides with SEQ ID NOS:9-12, the Bragg et al. reference discloses a *lef* sequence containing regions that are complementary to SEQ ID NOS:9-12.

Once again, the Examiner essentially reiterated the allegations discussed above, asserting that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the method of Ramisse et al. with the use of "functionally equivalent primers" selected from the sequence of Bragg et al. The Examiner also repeated the allegation that the Buck et al. reference expressly provides evidence of the equivalence of primers, and referred to *In re Deuel* (*supra*) to support the assertion that the claimed primers "simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of *B. anthracis*." Page 12 of the January 24, 2008 Office Action. Further, with respect to claims 92 and 93, the Examiner repeated the above rejections related to the Wittwer et al. and Qi et al references.

(D) Claim 96 stands rejected under 35 U.S.C. §103 as allegedly being unpatentable over the Ramisse et al. reference (*supra*), the Makino et al. reference (*supra*), the Price et al. reference (*supra*), the Bragg et al. reference (*supra*), and the Buck et al. reference (*supra*). The

[8] Bragg et al. (1989) *Gene* 81:45-54 (Exhibit G)

Examiner alleged that the Ramisse et al. reference teaches primers for detection of the *capB* gene, the *pag A* gene, and the *lef* gene. The Examiner alleged that while the Ramisse et al. reference does not specifically teach oligonucleotides with SEQ ID NO: 1-12, the Makino et al. reference discloses a *capB* sequence having regions that are complementary to SEQ ID NOS:1-4, the Price et al. reference discloses a *pagA* sequence containing regions that are complementary to SEQ ID NOS:5-8, and the Bragg et al. reference discloses a *lef* sequence containing regions that are complementary to SEQ ID NOS:9-12.

Again citing *In re Deuel* (*supra*), the Examiner alleged that the "claimed primers simply represent structural homologs" of prior art sequences, and asserted that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the method of Ramisse et al. with "functionally equivalent primers" selected from the sequences in any of the Makino et al., Price et al., and Bragg et al. references to arrive at the twelve specifically claimed oligonucleotides. Page 16 of the January 24, 2008 Office Action.

(7) Arguments

(A) The rejection of claims 57, 66, 67, 70, 79, 80, 83, 92, and 93 under 35 U.S.C. §103(a).

For the following reasons, the combination of cited references does not render obvious pending claims 57, 66, 67, 70, 79, 80, 83, 92, and 93.

First, the Examiner asserted that all primers and probes are equivalent and cited the Buck et al. reference to support this assertion. Buck et al. is a reference disclosing that a number of different sequencing primers were used successfully to sequence a particular target nucleic acid. The results of Buck et al., however, were not based on amplification reactions, did not use *capB*, *pagA*, or *lef* nucleic acid sequences, and did not even use *B. anthracis* nucleic acid sequences. Even ignoring the fact that Buck et al. does not use *B. anthracis* nucleic acid as the template, an automated sequencing reaction is significantly different from, for example, a PCR amplification reaction in which at least two oligonucleotides generally are used, or a real-time PCR amplification reaction in which at least four oligonucleotides generally are used. The results reported by Buck et al. using sequencing primers are not representative of results using different primer and probe sequences in various types of amplification reactions because, as Applicants have repeatedly argued, primer design for PCR amplification and primer and probe design for real-time PCR amplification is not always predictable.

In fact, Applicants have provided evidence of the unpredictability of primer and probe design. Significantly, and contrary to the Examiner's assertions, the guidelines published by the University of Chicago Cancer Research Center DNA Sequencing Facility state that one should "…be aware that no set of guidelines will always accurately predict the success of a primer. Some primers may fail for no apparent reason, and primers that appear to be poor candidates may work well."[9] In addition to the University of Chicago DNA Sequencing Facility guidelines, Applicants have made of record a number of peer-reviewed publications that compare different primer sets or compare the same primer set under different amplification conditions. For example:

[9] http://cancer-seqbase.uchicago.edu/primers.html (Exhibit H)

- the Csordas et al. reference[10] states that "[p]rimers originally designed for end-point PCR did not have adequate specificity or sensitivity compared with those specifically designed for real-time PCR"[11] (see, the Abstract);
- the Elnifro et al. reference[12] states that "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design" (see, the first full sentence at page 560);
- the Tichopad et al. reference[13] states that "unknown tissue-specific factors can influence amplification kinetics but this affect can be ameliorated, in part, by appropriate primer selection" (see, the Abstract); and
- the Abd-Elsalam reference[14] states that "…the most critical parameter for successful PCR is the design of primers" (see, the first full paragraph at page 94).

These references support Applicants' assertion that all primers and probes are not equivalent and may not work in an amplification reaction. It is noteworthy that a number of these references were published after Applicants' 2001 priority date, indicating that the state of the art, even after the present application was filed, was such that primer and probe design was not predictable.

Applicants' arguments are consistent with the Courts' recent decisions under 35 U.S.C. §103. Under the obviousness standard recently clarified by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*[15], such evidence of unpredictability strongly argues against the Examiner's obviousness rejections. As held by the Supreme Court in *KSR*:

> When there are a *finite* number of identified, *predictable* solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the *anticipated* success, it is likely the product not of innovation but of ordinary skill and common sense (emphasis added).

Such is not the case in the present application; the "known options" in the prior art are not "finite, identified, and predictable". In addition, none of the cited references, alone or in combination, provide the "anticipated success" referred to in *KSR*. As stated by the Court in

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[10] Csordas et al. (2004) *Lett. App. Microbiol.* 39:187-193 (Exhibit I)
[11] For the convenience of the Board, Applicants note that end-point PCR corresponds to conventional PCR and utilizes two primers while real-time PCR utilizes two primers and two probes.
[12] Elnifro et al. (2000) *Clin. Microbiol. Rev.* 13:559-570 (Exhibit J)
[13] Tichopad et al. (2004) *Mol. Cell. Probes* 18:45-50 (Exhibit K)
[14] Abd-Elsalam (2003) *African J. Biotech.* 2:91-95 (Exhibit L)
[15] *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007)

Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.[16], "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness."

To further support the rejection, the Examiner asserted that the claimed primer and probe sequences represent "structural homologs" of prior art sequences, and the Examiner cited *In re Deuel* to support this assertion. That is, according to the Examiner, the *capB*, *pagA*, and *lef* oligonucleotide sequences disclosed by Ramisse et al. are "structural homologs" of the presently claimed primer and probe sequences, even though Ramisse et al. does not disclose any of the presently claimed sequences. Contrary to the Examiner's assertion, *In re Deuel* does not indicate that two oligonucleotides that have different sequences but are complementary to the same target sequence are "structural homologs." *In re Deuel* held that claimed nucleic acid sequences were not obvious over prior art references that disclosed partial amino acid sequences encoded by such nucleic acid sequences and, therefore, *In re Deuel* is not germane to claims reciting specific nucleotide sequences such as those in the present case.

In addition, *In re Deuel* does not indicate that a primer or probe sequence that is complementary to a portion of a larger sequence is a "structural homolog," and Applicants are aware of no case law that stands for the proposition that a longer sequence makes *per se* obvious specific primer and probe sequences from within that longer sequence. Applicants understand that a longer sequence can be viewed as representing a very large genus of possible sub-sequences from which appropriate primers and probes can be selected. However, based on current case law, each of the claimed primer and probe sequences is not obvious over sequences disclosed in the cited references, and the particular combinations of four sequences that are claimed are certainly not obvious over sequences disclosed in the cited references. See, for example, *In re Bell*,[17] in which the Court held that "given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities [to select], the claimed sequences would not have been obvious." Further, *t*he

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[16] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364, 86 USPQ2d 1196 (Fed. Cir. 2008)

[17] *In re Bell* 991, F.2d 781, 784, 26 USPQ2d 1529 (Fed. Cir. 1993)

lack of motivation to select a particular DNA sequence from among numerous degenerate variants was a factor in determining the non-obviousness of the claims in *In re Deuel*.

As the Board is aware, a number of decisions, including those discussed herein, indicate that a species (e.g., a particular oligonucleotide) is not obvious over a very large genus (in this case, all possible fragments of the full-length sequence disclosed in the reference to which the oligonucleotide has complementarity). Applicants note that much of the case law regarding the non-obviousness of a species over the prior art teaching of a genus containing such a species (sometimes referred to as an "invention of selection") is in the chemical arts. Significantly, the Courts have stated in several major opinions that DNA is a chemical. See, for example, *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*,[18] in which the Court stated that "a gene is a chemical compound." As such, each of the pending independent claims recite four different specific chemical species.

Applicants believe the record amply supports the argument of nonobviousness. However, objective evidence of nonobviousness, which, according to *Ortho-McNeil v. Mylan*[19], "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness", also has been provided. For example, the sequences recited in the present claims exhibit high sensitivity and specificity toward their targets. See, for example, Examples 1, 4, and 5 of Applicants' specification. In addition, each of the claimed probe sequences (SEQ ID NOS:3, 4, 7, 8, 11 and 12) has a particular melting temperature that was identified and is disclosed in the specification. The particular melting temperatures can be used as confirmation of the presence or absence of *B. anthracis* in a sample. Therefore, the claimed probe sequences can be used to further increase the accuracy of detecting *B. anthracis*. See, for example, page 23, lines 5-7 and Example 3 of the specification. Thus, the exceptional sensitivity and specificity of the claimed combinations was unexpected. According to *KSR*[20], 35 U.S.C. §103 does not bar patentability where, as here, the claimed invention presents an unpredictable variation of the prior art and operates in an "unexpected and fruitful manner."

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[18] *Amgen, Inc. v.Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016 (Fed. Cir. 1991)
[19] *Supra* at 1365
[20] *Supra* at 1740

In summary, Courts have long held that species (in the present case, the specific oligonucleotides recited in the pending claims) are not obvious over a very large genus (in the present case, the full-length gene sequence to which the oligonucleotides have complementarity). Applicants also have provided evidence that, even after the application was filed, there was unpredictability in primer and probe design, particularly for PCR and real-time PCR reactions. Given the disclosures of Ramisse et al., Makino et al., Price et al. and Bragg et al., one of ordinary skill in the art would not have been able to predictably modify the disclosed sequences, even in view of Buck et al., to arrive at the claimed combination of two primers and two probes having the ability to specifically amplify and detect *B. anthracis* DNA by real-time PCR as do the claimed primers and probes. Further, Applicants have provided independent evidence in the form of secondary considerations that render the claims nonobvious.

Thus, for at least the reasons set forth herein, the primer and probe sequences recited in present claims 57, 66, 67, 70, 79, 80, 83, 92, and 93 are not obvious over the combination of cited references. Accordingly, Applicants respectfully request that the Board overturn the rejection of these claims under 35 U.S.C. §103(a).

(B) The rejection of claim 96 under 35 U.S.C. §103(a).

Claim 96 is directed toward an article of manufacture that includes all four *capB* primers and probes (SEQ ID NOS:1-4), all four *pagA* primers and probes (SEQ ID NOS:5-8), and all four *lef* primers and probes (SEQ ID NOS:9-12).

The Ramisse et al., Makino et al., Price et al., Bragg et al., and Buck et al. references are discussed above. None of these references teaches or suggests any of the *twelve* specific primer or probe sequences recited in claim 96. The arguments herein regarding the Examiner's assertions with respect to *In re Deuel* and "structural homologs" are reiterated with respect to the rejection of this claim.

Applicants fail to understand how a claim reciting *twelve* very specific primer and probe sequences to three different gene targets can be obvious over the cited art. As indicated herein, a combination of four claimed primer and probe sequences is not obvious over the cited references, and certainly not the particular combination of *twelve* primer and probe sequences recited in claim 96.

In addition, as indicated herein, Applicants have presented evidence of secondary considerations with respect to the unexpectedly high sensitivity and specificity of the presently claimed primers and probes.

Accordingly, Applicants respectfully request withdrawal of the rejection of claim 96 under 35 U.S.C. § 103(a).

Conclusion

Each of independent claims 57, 70, and 83 recites the particular sequence of two primers and two probes, while independent claim 96 recites the particular sequences of six primer and six probes. The claimed combinations of sequences are not obvious over the cited sequences in view of Buck et al. Therefore, the independent claims and those depending therefrom are not obvious over the cited references.

Please charge $540 for the brief fee, and apply any other charges or credits, to Deposit Account No. 06-1050.

Respectfully submitted,

/February 20, 2009/

Date:_____

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Appendix of Claims

57. An article of manufacture, comprising:

a pair of *capB* primers, wherein said pair of *capB* primers comprises a first *capB* primer and a second *capB* primer, wherein said first *capB* primer consists of the sequence 5'-CCC AAT TCG AGT AAA CAT A-3' (SEQ ID NO:1) and wherein said second *capB* primer consists of the sequence 5'- ACT GCC ATA CAT TCA CAA -3' (SEQ ID NO:2);

a pair of *capB* probes, wherein said pair of *capB* probes comprises a first *capB* probe and a second *capB* probe, wherein said first *capB* probe consists of the sequence 5'- CGA TTA AGC GCC GTA AAG AAG GTC CTA ATA TC -3' (SEQ ID NO:3) and wherein said second *capB* probe consists of the sequence 5'- GTG AGC AAC GCA GGG TAG TTA AAG AGG CTG -3' (SEQ ID NO:4); and

a donor fluorescent moiety and a corresponding acceptor fluorescent moiety.

66. The article of manufacture of claim 57, wherein said first *capB* probe is labeled with said donor fluorescent moiety and said second *capB* probe is labeled with said corresponding acceptor fluorescent moiety.

67. The article of manufacture of claim 57, further comprising a package label or package insert having instructions thereon for using said pair of *capB* primers and said pair of *capB* probes to detect the presence or absence of *B. anthracis* in a biological sample.

70. An article of manufacture, comprising

a pair of *pagA* primers, wherein said pair of *pagA* primers comprises a first *pagA* primer and a second *pagA* primer, wherein said first *pagA* primer consists of the sequence 5'-TAC AGG

ACG GAT TGA TAA G-3' (SEQ ID NO:5) and wherein said second *pagA* primer consists of the sequence 5'- TTT CAG CCC AAG TTC TTT -3' (SEQ ID NO:6);

a pair of *pagA* probes, wherein said pair of *pagA* probes comprises a first *pagA* probe and a second *pagA* probe, wherein said first *pagA* probe consists of the sequence 5'- AGT ACA TGG AAA TGC AGA AGT G -3' (SEQ ID NO:7) and wherein said second *pagA* probe consists of the sequence 5'- ATG CGT CGT TCT TTG ATA TTG GT -3' (SEQ ID NO:8); and

a donor fluorescent moiety and a corresponding acceptor fluorescent moiety.

79. The article of manufacture of claim 70, wherein said first *pagA* probe is labeled with said donor fluorescent moiety and said second *pagA* probe is labeled with said corresponding acceptor fluorescent moiety.

80. The article of manufacture of claim 70, further comprising a package label or package insert having instructions thereon for using said pair of *pagA* primers and said pair of *pagA* probes to detect the presence or absence of *B. anthracis* in a biological sample.

83. An article of manufacture, comprising

a pair of *lef* primers, wherein said pair of *lef* primers comprises a first *lef* primer and a second *lef* primer, wherein said first *lef* primer consists of the sequence 5'-TTT TAC CGA TAT TAC TCT CC-3' (SEQ ID NO:9) and wherein said second *lef* primer consists of the sequence 5'- AAC CTA AAG GCT TCT GC -3' (SEQ ID NO:10);

a pair of *lef* probes, wherein said pair of *lef* probes comprises a first *lef* probe and a second *lef* probe, wherein the first *lef* probe consists of the sequence 5'- ATT AAG GAA TGA TAG TGA GGG T -3' (SEQ ID NO:11) and wherein said second *lef* probe consists of the

sequence 5'- TAT ACA CGA ATT TGG ACA TGC T -3' (SEQ ID NO:12); and

a donor fluorescent moiety and a corresponding acceptor fluorescent moiety.

92. The article of manufacture of claim 83, wherein said first *lef* probe is labeled with said donor fluorescent moiety and said second *lef* probe is labeled with said corresponding acceptor fluorescent moiety.

93. The article of manufacture of claim 83, further comprising a package label or package insert having instructions thereon for using said pair of *lef* primers or said pair of *lef* probes to detect the presence or absence of *B. anthracis* in a biological sample.

96. An article of manufacture comprising a pair of *capB* primers and a pair of *capB* probes, wherein said pair of *capB* primers comprises a first *capB* primer and a second *capB* primer, wherein said pair of *capB* probes comprises a first *capB* probe and a second *capB* probe, wherein said first *capB* primer consists of the sequence 5'-CCC AAT TCG AGT AAA CAT A-3' (SEQ ID NO:1), wherein said second *capB* primer consists of the sequence 5'-ACT GCC ATA CAT TCA CAA-3' (SEQ ID NO:2), wherein said first *capB* probe consists of the sequence 5'-CGA TTA AGC GCC GTA AAG AAG GTC CTA ATA TC-3' (SEQ ID NO:3), wherein said second *capB* probe consists of the sequence 5'-GTG AGC AAC GCA GGG TAG TTA AAG AGG CTG-3' (SEQ ID NO:4), said article of manufacture further comprising a pair of *pagA* primers and a pair of *pagA* probes, wherein said pair of *pagA* primers comprises a first *pagA* primer and a second *pagA* primer, wherein said pair of *pagA* probes comprises a first *pagA* probe and a second *pagA* probe, wherein said first *pagA* primer consists of the sequence 5'-TAC AGG ACG GAT TGA TAA G-3' (SEQ ID NO:5), wherein said second *pagA* primer consists of the

sequence 5'-TTT CAG CCC AAG TTC TTT-3' (SEQ ID NO:6), wherein said first *pagA* probe consists of the sequence 5'-AGT ACA TGG AAA TGC AGA AGT G- 3' (SEQ ID NO:7), wherein said second *pagA* probe consists of the sequence 5'-ATG CGT CGT TCT TTG ATA TTG GT- 3' (SEQ ID NO:8), said article of manufacture further comprising a pair of *lef* primers and a pair of *lef* probes, wherein said pair of *lef* primers comprises a first *lef* primer and a second *lef* primer, wherein said pair of *lef* probes comprises a first *lef* probe and a second *lef* probe, wherein said first *lef* primer consists of the sequence 5'-TTT TAC CGA TAT TAC TCT CC-3' (SEQ ID NO:9), wherein said second *lef* primer consists of the sequence 5'-AAC CTA AAG GCT TCT GC-3' (SEQ ID NO:10), wherein said first *lef* probe consists of the sequence 5'-ATT AAG GAA TGA TAG TGA GGG T- 3' (SEQ ID NO:11), wherein said second *lef* probe consists of the sequence 5'-TAT ACA CGA ATT TGG ACA TGC T- 3' (SEQ ID NO:12).

Evidence Appendix

Exhibit	Document	Date Entered
A	Ramisse et al. (1996) *FEMS Microbiology Letters* 145:9-16 (Exhibit A)	Cited by Examiner in Office Action mailed January 30, 2004
B	Makino et al. (1989) *J. Bacteriol.* 171:722-30 (Exhibit B)	Cited by Examiner in Office Action mailed January 30, 2004
C	Buck et al. (1999) *Biotechniques* 27:528-36 (Exhibit C)	Cited by Examiner in Office Action mailed January 30, 2004
D	Wittwer et al. (1997) *Biotechniques* 22:130-138	Cited by Examiner in Office Action mailed January 30, 2004
E	Qi et al. (2001) *Appl. Env. Microbiol.* 67:3720-3727	Cited by Examiner in Office Action mailed January 30, 2004
F	Price et al. (1999) *J. Bacteriol.* 181:2358-2362	Cited by Examiner in Office Action mailed January 30, 2004
G	Bragg et al. (1989) *Gene* 81:45-54	Cited by Examiner in Office Action mailed January 30, 2004
H	http://cancer-seqbase.uchicago.edu/primers.html	Submitted by Applicants with Request for Continued Examination filed November 7, 2005
I	Csordas et al. (2004) *Lett. App. Microbiol.* 39:187-193	Submitted by Applicants with Request for Continued Examination filed November 7, 2005
J	Elnifro et al. (2000) *Clin. Microbiol. Rev.* 13:559-570	Submitted by Applicants with Request for Continued Examination filed November 7, 2005
K	Tichopad et al. (2004) *Mol. Cell. Probes* 18:45-50	Submitted by Applicants with Request for Continued Examination filed November 7, 2005
L	Abd-Elsalam (2003) *African J. Biotech.* 2:91-95	Submitted by Applicants with Request for Continued Examination filed November 7, 2005

Related Proceedings Appendix

None.